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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,678	05/01/2007	Kathryn E. Uhrich	01435.035US1	8472

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EXAMINER	
ORWIG, KEVIN S	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
12/14/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,678	UHRICH ET AL.	
	Examiner	Art Unit	
	Kevin S. Orwig	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8-23,88,240 and 241* is/are pending in the application.

4a) Of the above claim(s) *88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8-23,240 and 241* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/3/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. The arguments filed on Dec. 3, 2010 have been entered.

Status of the Claims

Claims 1, 2, 8-23, 88, 240, and 241 are pending. Claims 3-7, 24-87, and 89-239 were previously cancelled. Claim 88 is withdrawn. No claims have been amended; no claims have been added. Claims 1, 2, 8-23, 240, and 241 are now under consideration. This Office Action is in response to the request for continued examination filed on Dec. 3, 2010.

OBJECTIONS/REJECTIONS MAINTAINED

The rejection of claims 1, 2, 8-23, 240 and 241 under 35 U.S.C. 103(a) over TIAN and UHRICH is maintained as discussed below.

Claim Rejections - 35 USC § 103 (Maintained)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 8-23, 240 and 241 are rejected under 35 U.S.C. 103(a) as being unpatentable over TIAN (Tian *et al.* Polymer Preprints (2002) 43(2); 719-720; of

record) in view of UHRICH (WO 03/005959; Published Jan. 23, 2003; on IDS dated Nov. 17, 2006, of record).

1. Tian discloses amphiphilic molecules of the structure depicted in formula III of instant claim 22 (elected species) that form stable polymeric micelles (p. 719, left col., 2nd par.; Scheme 1; 1st par. of Results and Discussion section). Tian teaches that these molecules are intermediates in the preparation of amphiphilic star-like macromolecules (ASMs) (2nd par. of Introduction). Tian teaches that these micelles have hydrophobic cores suitable as "microcontainers" for lipophilic compounds and that the hydrophilic/lipophilic ratios (HLB) can be controlled by changing the length of the PEG or acyl chains (first pars. of Introduction and Results and Discussion sections). Tian teaches that the micelles form 20 nm diameter aggregations (i.e. nanoparticulates).

2. While Tian discloses the molecules of applicants' elected species, and suggests that they have utility for the encapsulation of hydrophobic compounds, Tian does not explicitly teach the use of these compounds to remove low-density lipoproteins (LDL) or to treat atherosclerosis. Since Tian does not specifically disclose what types of molecules may be encapsulated within the micelles, one would be motivated to look to the related literature for guidance regarding their usage.

3. Uhrich discloses polymeric compounds that form stable micelles in solution, wherein the micelles have a hydrophobic core and act as microcontainers for lipophilic compounds (abstract; 1st par. on p. 2). Just as the molecules of Tian, the hydrophobicity of Uhrich's compounds can be controlled by changing the length of the PEG or acyl chains (2nd par. on p. 34). Uhrich teaches that these micelles are

particularly useful for solubilizing hydrophobic molecules (p. 26, 1st par.; and p. 34, last par.). Uhrich teaches the use of these compounds to sequester lipoproteins such as LDL that contribute to atherosclerosis (page 10, 4th par., elements (a) and (c)) by administering them to a patient in need of reducing the concentration of lipoproteins (p. 10, end of 4th par.). Uhrich teaches that such administration can minimize cardiovascular diseases, such as atherosclerosis, caused by the presence of excess LDL in the blood (p. 10, end of 4th par.).

4. Uhrich discloses embodiments of the compounds wherein they may contain the molecules taught by Tian (i.e. the instantly claimed molecules) as a part of their structure. For example, see Scheme 2 (top of p. 26), which discloses non-PEGylated versions of the instantly claimed molecules. It is noted that Uhrich teaches the use of polyethylene glycol (i.e. PEGylation) with these molecules (p. 29, 2nd par.). Additionally, Figure 10 teaches an embodiment wherein four of Tian's molecules are incorporated into a polyol core, the only difference from Tian's compounds being that the embodiment depicted in the figure contains an amide instead of an ester linkage between the mucic acid moiety and the mPEG moiety. It is noted that replacement of this amide by an ester is taught in Uhrich's disclosure (see description of the compounds on pages 2-8, particularly embodiment d) on p. 7, and the description of R^4 in this embodiment on p. 8). Thus, consistent with Tian's teaching, Tian's molecules are intermediates in the ASMs of Uhrich.

5. Given the similarity of the micelles formed by each of these molecules, and their identical intended uses to encapsulate hydrophobic compounds, it would have been

prima facie obvious to one of ordinary skill in the art at the time of the invention to utilize the molecules of Tian to treat atherosclerosis by sequestering or removing LDL as taught by Uhrich. One would have been motivated to do so since Tian suggests that the molecules are suitable for use with hydrophobic compounds, but does not teach which specific compounds are suitable. Given Uhrich's disclosure, the ordinary artisan would have readily envisioned the use of Tian's intermediates in the same manner as the macromolecular ASMs of Uhrich. Further, the artisan would be motivated to use Tian's molecules since they are simpler than those of Uhrich and therefore would be easier and cheaper to prepare. The similarity of the micelles and use of both Tian's intermediates and Uhrich's ASMs would have provided the artisan with a high expectation that Tian's molecules would function in a substantially similar way and be useful in the treatment of atherosclerosis by sequestering LDL in the hydrophobic core. This is especially true given the direct teachings of both Tian and Uhrich that micelles of each of the disclosed compounds function in the same way, namely forming structures suitable for carrying lipophilic compounds. Thus, claims 1, 2, 8-23, 240, and 241 are obvious over Tian and Uhrich.

Regarding the obviousness rejections herein, it is noted that a reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of

the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, in the absence of evidence to the contrary, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

Applicants' arguments have been fully considered but are not persuasive. Applicants assert that there are differences between the references (response, p. 7-8).

This argument is unpersuasive for at least the following reasons. First, no distinction between the structures taught by Tian and Uhrich appears in the instant claims. In response to applicants' argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the differences noted as elements 1) through 6) on p. 7 of the response) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Second, no objective evidence has been provided to establish any material difference between the structures taught by Tian and Uhrich (i.e. elements 1) through 6) on p. 7 of the response). It is well established that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney

argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See MPEP § 716.01(c)(II). See also MPEP § 2145, which states, "...arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984)." If a *prima facie* case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie* case. See, e.g., *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Applicants have provided no evidence to support the assertions made in the response, and have not rebutted the *prima facie* case of obviousness that has been established.

The noted lack of evidence is critical because applicants appear to be mischaracterizing Uhrich's teachings. For example, applicants assert that the macromolecules of Uhrich *are* micelles (response, p. 7). But that is not taught by Uhrich. For example, the term "unimolecular" appears once in Uhrich's entire disclosure:

> "Using the equation of the lidocaine calibration curve, the amount of lidocaine entrapped in the unimolecular micelle core was determined." (p. 34, lines 11-13)

Does this single mention of the term "unimolecular" indicate that each of the macromolecules described by Uhrich forms its own micelle? Certainly not. If that is what is intended by Uhrich, it is not made clear anywhere in the reference. In fact, Uhrich teaches the opposite at p. 26, lines 5-7, which states:

> "Thus, according to one embodiment of the present invention, a therapeutic agent is encapsulated by combining the agent and a **plurality** of compounds of formula (I) in a solvent, such as water." (emphasis added)

See also

> "The invention also provides a method for preparing an encapsulate of the invention comprising combining compounds of formula (I) and a molecule (e.g., a therapeutic agent) in a solvent, and allowing **the compounds of formula (I) to aggregate around the molecule**, to provide the encapsulate (i.e., the 15 molecule surrounded or partially surrounded by **compounds** of formula (I))." (p. 9, lines 11-15; emphasis added)

It is noted that formula I includes the polyol linker that is lacking in Tian's molecules. Thus, Uhrich directly teaches that a *plurality* of these molecules aggregating around a hydrophobic compound is required to form an encapsulating structure (i.e. a micelle). This is exactly the same situation as is taught by Tian. Regardless, even if applicants had provided evidence to show that the polyol-linked molecules actually do form individual "unimolecular" micelles, that would still not establish non-obviousness of using Tian's molecules in the way suggested by Uhrich because, both Tian and Uhrich teach that the molecules, both the intermediate "monomers" of Tian and the covalently linked "polymeric" forms of Uhrich, function in *precisely the same way*, forming stable micelles in solution that have a hydrophobic core and act as microcontainers for lipophilic compounds. Thus, even if, *in arguendo*, the polyol-linked molecules of Uhrich were established to be unimolecular micelles (and they have not been), it would not matter because one of skill in the art would have a reasonable expectation of success in

using Tian's molecules in the same way as Uhrich's, based on the direct teachings of both references. Similar reasoning holds for all of the alleged differences alleged by applicants on p. 7 of the response.

Applicants allege that the examiner failed to explain why the molecules of Tian and Uhrich are similar (response, bridging pgs. 7-8).

That is not true. Applicants are directed to pars. 1-3 of the prior Office Action where the similarities of the two molecules are discussed in detail. For example, Tian teaches that the compounds form micelles have hydrophobic cores suitable as “microcontainers” for lipophilic compounds and that the hydrophilic/lipophilic ratios (HLB) can be controlled by changing the length of the PEG or acyl chains, which is identical to Uhrich's teaching does (see Uhrich at: abstract; 1st par. on p. 2; 2nd par. on p. 34; p. 26, 1st par.; and p. 34, last par.). In fact the molecules taught by both Tian and Uhrich are functionally identical. Additionally, Uhrich states that, "Accordingly, the invention provides a compound of formula (I) as described above. Such compounds of formula (I) are useful intermediates for preparing micelles that can be used in drug delivery applications and that can be cross-linked to provide cross-linked macromolecules that are also useful in drug delivery applications." (p. 9, lines 4-8). The functional similarity provides an artisan with a high expectation of success in using the molecules of Tian in the methods suggested by Uhrich.

Applicants assert that Tian provides "No disclosure of encapsulation of any agents" (response, p. 8).

This is incorrect. Applicants are directed to Scheme 1 of Tian, which illustrates a

drug encapsulated within the micelle.

Applicants assert that Uhrich states that the ASM molecules do not aggregate, referring to Uhrich at p. 34, lines 23-27 (response, p. 8).

Again, applicants mischaracterize Uhrich. Applicants are directed to Uhrich at p. 9, lines 11-15:

> "The invention also provides a method for preparing an encapsulate of the invention comprising combining compounds of formula (I) and a molecule (e.g., a therapeutic agent) in a solvent, and allowing **the compounds of formula (I) to aggregate around the molecule**, to provide the encapsulate (i.e., the 15 molecule surrounded or partially surrounded by **compounds** of formula (I))." (p. 9, lines 11-15; emphasis added)

Clearly, the molecules of Uhrich aggregate around the hydrophobic molecule that they encapsulate, as directly taught by Uhrich AND Tian. It is submitted that any ordinary artisan would understand the reference to the lack of aggregation by Uhrich at p. 34, lines 23-27 to refer to a lack of aggregation of the micelles overall, not the individual macromolecules that must aggregate to encapsulate a hydrophobic agent. That is, the PEG-coated micelles to not stick to *one another*, which would be problematic for drug formulation and delivery.

Applicants again argue that the molecules of Uhrich are different than those of Tian by virtue of the presence of the small polyol/polyacid core (response, p. 9).

This argument is unpersuasive at least because Tian teaches the exact species instantly elected. In response to applicant's argument that the molecules of Uhrich are slightly different, being linked by a small polyol/polyacid moiety, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined

teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Moreover, as stated above, applicants provide no evidence that the small polyol/polyacid core causes Uhrich's to function in a different way than those of Tian. In fact, the teachings of Uhrich establish that they function in the same way as those of Tian.

Applicants assert that the combination of Tian and Uhrich is improper (response, p. 10).

The above discussion is incorporated herein. The combination of Tian and Uhrich is clearly proper, and applicants have not shown otherwise.

Conclusion

Claims 1, 2, 8-23, 240, and 241 are rejected. No claims are currently allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin S. Orwig whose telephone number is (571)270-5869. The examiner can normally be reached IFP4:00 pm (with alternate Fridays off). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached IFP:00 pm at (571)272-06140614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KSO/

/Allison M. Ford/
Primary Examiner, Art Unit 1651